Beryllium Sensitization Progresses to Chronic Beryllium Disease

A Longitudinal Study of Disease Risk

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The blood beryllium lymphocyte proliferation test is used in medical surveillance to identify both beryllium sensitization and chronic beryllium disease. Approximately 50% of individuals with beryllium sensitization have chronic beryllium disease at the time of their initial clinical evaluation; however, the rate of progression from beryllium sensitization to chronic beryllium disease is unknown. We monitored a cohort of beryllium-sensitized patients at 2-year intervals, using bronchoalveolar lavage and repeated transbronchial lung biopsies to determine progression to chronic beryllium disease as evidenced by granulomatous inflammation in lung tissue. Fifty-five individuals with beryllium sensitization were monitored with a range of **2 to 5** clinical evaluations. Disease developed in 17 sensitized individuals **(31%) within** an average follow-up period of 3.8 years (range, 1.0-9.5 years). Thirty-eight of the **55 (69%)** remained beryllium sensitized without disease after an average follow-up time of 4.8 years (range, 1.7-11.6 years). Progressors were more likely to have worked as machinists. We found no difference in average age, sex, race or ethnicity, smoking status, or beryllium exposure time between those who progressed to chronic beryllium disease and those who remained sensitized without disease. We conclude that beryllium sensitization is an adverse health effect in beryllium-exposed workers and merits medical follow-up.

Keywords: berylliosis; beryllium; lymphocyte proliferation test; medical surveillance; transbronchial biopsy

In the late 1980s and 1990s, several population-based studies of beryllium-exposed workers in the beryllium ceramics and nuclear weapons industries resulted in the resurrected use of a blood test designed to detect beryllium-specific T cell-proliferative responses in the blood of beryllium-exposed workers (1-9). This test, referred to as the beryllium lymphocyte proliferation test (BeLPT), has been shown to have greater sensitivity and specificity than previously used medical surveillance tools to detect beryllium sensitization (BeS) and chronic beryllium disease (CBD). The test has been shown to outperform chest radiograph, simple spirometry, and clinical examination in the detection of both BeS and CBD (4, 6, 8). The blood BeLPT is now the standard of care in workplace screening and surveillance efforts (9-11) identifying both BeS and CBD. Among workers identified with BeS based on abnormal blood BeLPT results, clinical evaluation with bronchoalveolar lavage and transbronchial lung biopsy is usually necessary to confirm the diagnosis of CBD.

The percentage of those with BeS who have CBD at the time of initial evaluation varies among different workforce studies (1, 3-5, 7, 9, 10). Within these mainly cross-sectional studies, the rate of CBD among those with BeS varied from 14 to 100%. In a report of beryllium ceramic workers by Kreiss and coworkers (4), 100% of workers with abnormal blood BeLPT results had CBD on clinical evaluation, some of whom were clinically symptomatic. Beryllium was used historically in that plant, with its use ending 15 years before the surveillance project was initiated. The mean time from first exposure to screening among the study participants was 24 years. In contrast, Henneberger and coworkers (10) identified only one employee with CBD among seven sensitized short-term workers (14.3%) of a beryllium ceramics facility. In that cohort, the median time from first beryllium exposure to time of blood screening was only 1 year (range, 0.25-12.75 years). The authors speculated that a certain lung burden of beryllium may be necessary to result in CBD or that BeS progresses to disease with the passage of time, regardless of lung burden or continued exposure. Longitudinal follow-up of their cohort will be of interest to determine whether those with BeS without disease progress to CBD as the latency period from first exposure increases. As a result, when conducting blood testing for beryllium-exposed workers, it is not always possible to know whether individuals with abnormal BeLPT results have BeS alone or already have CBD.

The merits of the blood BeLPT as a biomarker of beryllium health effect hinge, in part, on whether the blood test detects a clinically significant abnormality or not. The blood BeLPT has proven utility for those patients with clinical evidence of lung disease by lending specificity to their diagnosis. However, counseling of individuals with abnormal blood BeLPT results, in whom disease signs and symptoms are not obvious, would be greatly enhanced by knowing the rate at which those who do not have CBD at the time of initial evaluation develop disease. We have previously demonstrated that BeS precedes CBD (3), but the natural history and rate of progression from sensitization to disease are not fully known (12) because the literature to date has focused on cross-sectional, and not longitudinal, study designs.

We hypothesize that most beryllium-sensitized workers will eventually develop CBD evidenced by noncaseating granulomas and/or mononuclear cell infiltrates in lung tissue. To test this hypothesis, we performed a longitudinal cohort study of a group of individuals detected through workplace medical surveillance programs as having BeS with no initial evidence of CBD. We have studied these individuals at 2-year intervals for indication of disease progression as evidenced by the new development of granulomatous inflammation detected by lung biopsy. Some of the results of this study have been previously reported in the form of an abstract (13).

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